NTP
National Toxicology Program

Report on Carcinogens
Draft Substance Profile for Cobalt-Tungsten Carbide: Hard Metals and Powders

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Outline

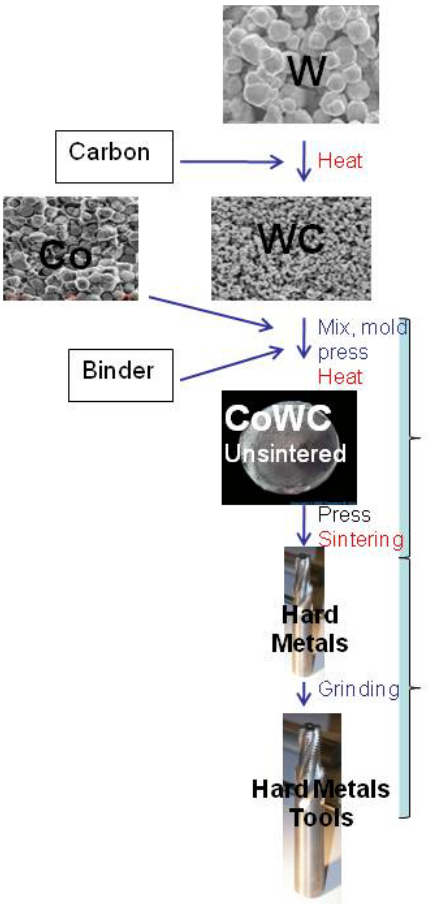
- Properties and use
- Exposure
- Proposed listing
- Evidence of carcinogenicity
  - Cancer studies in humans
  - Mechanistic studies of carcinogenicity
  - No cancer studies in experimental animals

Properties and Use

- Cobalt-tungsten carbide
  - Composites of tungsten carbide particles with a metallic cobalt powder binder
- Hard metals are produced by pressing the composites into a compact solid at high temperature by a process known as sintering
- Listing includes hard metals, powders and dusts that contain both cobalt and tungsten carbide
- Used primarily for cutting tools
  - Hard metals are characterized by extreme hardness, abrasion resistance and toughness

Significant U.S. Exposure

- Production
  - U.S. domestic production of hard metal products was estimated at 6,080 tons in 2004.
- Exposure
  - Occupational: primarily via inhalation or dermal
    - Hard metal manufacturing
    - Recycling of hard metal products
    - Grinding and sharpening of hard metal tools
    - Negligible exposure to other end-users
  - General population: living in the vicinity of hard metal production or maintenance facilities
    - High levels of cobalt detected in soil near carbide tool-grinding plant
    - Cobalt and tungsten detected in air near manufacturing plant; plant may have been source



Production and Exposure to Cobalt-Tungsten Carbide Hard Metals

Cobalt levels (µg/m^3)
Range of means across U.S. studies

Studies of pre-sintering & sintering operations
25–32,470

Higher exposure in pre-sintering & sintering process than post-sintering steps

Studies of post-sintering operations
Grinding:
27–280

Co = cobalt, W = tungsten, WC = tungsten carbide

Proposed Listing for Cobalt-Tungsten Carbide: Hard Metals and Powders

Cobalt-tungsten carbide: hard metals and powders are *reasonably anticipated to be human carcinogens*

- Limited evidence of carcinogenicity from studies in humans
- Supporting mechanistic evidence

Limited Evidence of Carcinogenicity from Studies in Humans

- Consistent findings of excess lung cancer mortality among cobalt-tungsten carbide hard metal manufacturing workers across studies
- Positive exposure-response relationships
- Risks not likely to be explained by confounding from tobacco smoking
- Limited number of studies; only one well-conducted study of an independent population

Epidemiological Studies

Study	Population	Analyses	Comments
Swedish multi-plant Hogstedt and Alexandersson 1990	3,163 men 3 plants	SMR Exposure level, duration & latency	Independent population
French multi-plant Moulin *et al.* 1998	7,549 men & women All 10 plants in France Nested case-control study of lung cancer 61 cases/180 controls	SMR Exposure-response analyses	Includes workers from Lasfargues and Wild
Small French plant Lasfargues *et al.* 1994	709 men	SMR Exposure level, duration & latency	Overlapping with Moulin *et al.*
Large French plant Wild *et al.* 2000	2,860 men & women Lung cancer - 2,216 men	SMR Workshop Exposure-response analyses	Overlapping with Moulin *et al.*

Study Characteristics: Moulin and Wild

- Job exposure matrix used to created semi-quantitative exposure scale for exposure to CoWC
  - Four exposure metrics evaluated:
    - Exposure level: highest score experienced during an individual's work history
    - Duration of exposure: at a level of 2 or higher
    - Unweighted cumulative dose: assigns same level to occasional and full time exposure, favors peak exposure
    - Frequency-weighted cumulative dose: exposure level weighted by the frequency of exposure
  - Limitation: not quantitative exposure assessment
  - Validation of exposure assessment with measurements of cobalt
- Analyses considered potential confounding by tobacco smoking or exposure to other occupational carcinogens
- Most informative study: Moulin *et al.*

Findings for Lung Cancer: Independent Populations

Study	Analyses	SMR or OR (95 % CI); exposed deaths	
Swedish Hogstedt and Alexandersson 1990	Total cohort 10 yr duration & 20 yr latency	1.34 (0.77–2.13); 17 2.78 (1.11–5.72); 7	
French Moulin *et al.* 1998	Total cohort (SMR) *Case control study* Score 2 + vs. 0 to 1* *Exposure-response* Highest score category Longest duration** Highest cum. dose Highest wgt. cum. dose	1.30 (1.00–1.66); 63 *OR (95% CI)* 1.93 (1.03–3.62); 35 2.79 (0.96–8.10); 8 2.03 (0.49–8.51); 4 4.13 (1.49–11.47); 23 2.73 (1.02–7.26); 19	 P_{trend} 0.08 0.03 0.01 0.08

* Adjusted for "other cobalt exposures" such as cobalt alone
** Among workers with exposure scores of 2 or greater

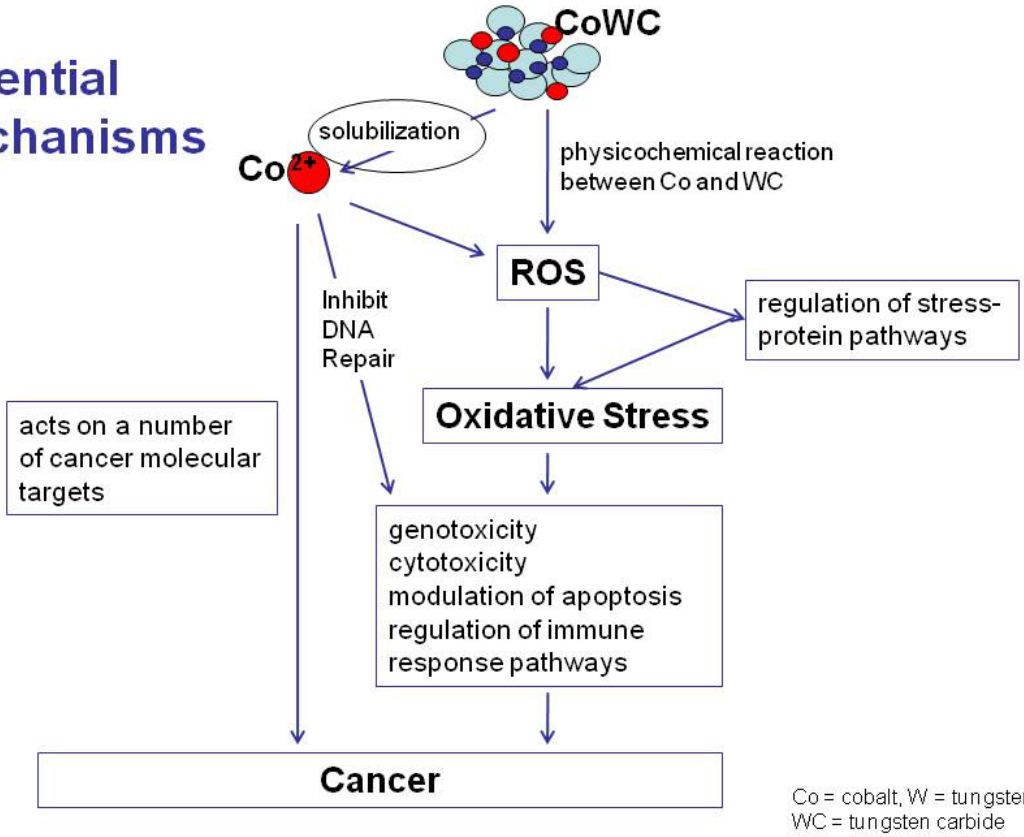
Studies of Individual Factories in the French Cohort

- Large factory (Wild)
  - Statistically significant risks found among
    - All male workers
    - Male workers ever employed in pre-sintering workshops
    - Male workers exposed to levels with a exposure score 2 or greater
    - Male workers in the highest category of cumulative exposure
  - Highest risk observed among workers in highest exposure category of all four exposure metrics although test for trends were not statistically significant in models adjusting for smoking and exposure to "IARC carcinogens"
- Small factory (Lasfargues)
  - Significant excess risk in overall population and among men with the highest exposure level

Confounding

- Moulin
  - Controlling for tobacco smoking or exposure to "IARC carcinogens" did not change risk estimates or trend values in exposure-response relationships
  - Little difference between the smoking-adjusted (OR = 2.6, 95% CI = 1.16 to 5.82) and unadjusted (OR= 2.29, 95% CI = 1.08 to 4.88) risk estimates for exposure to cobalt-tungsten carbide
  - No evidence of increased risk for smoking-related diseases such as chronic bronchitis and emphysema
- Other studies
  - Lasfargues and Swedish cohort: similar smoking habits in subset of workers as in the general population
  - Wild: significant association with duration of exposure to unsintered CoWC in models that controlled for smoking and exposure to "IARC carcinogens"

Potential Mechanisms



Co = cobalt, W = tungsten,
WC = tungsten carbide
ROS = reactive oxygen species

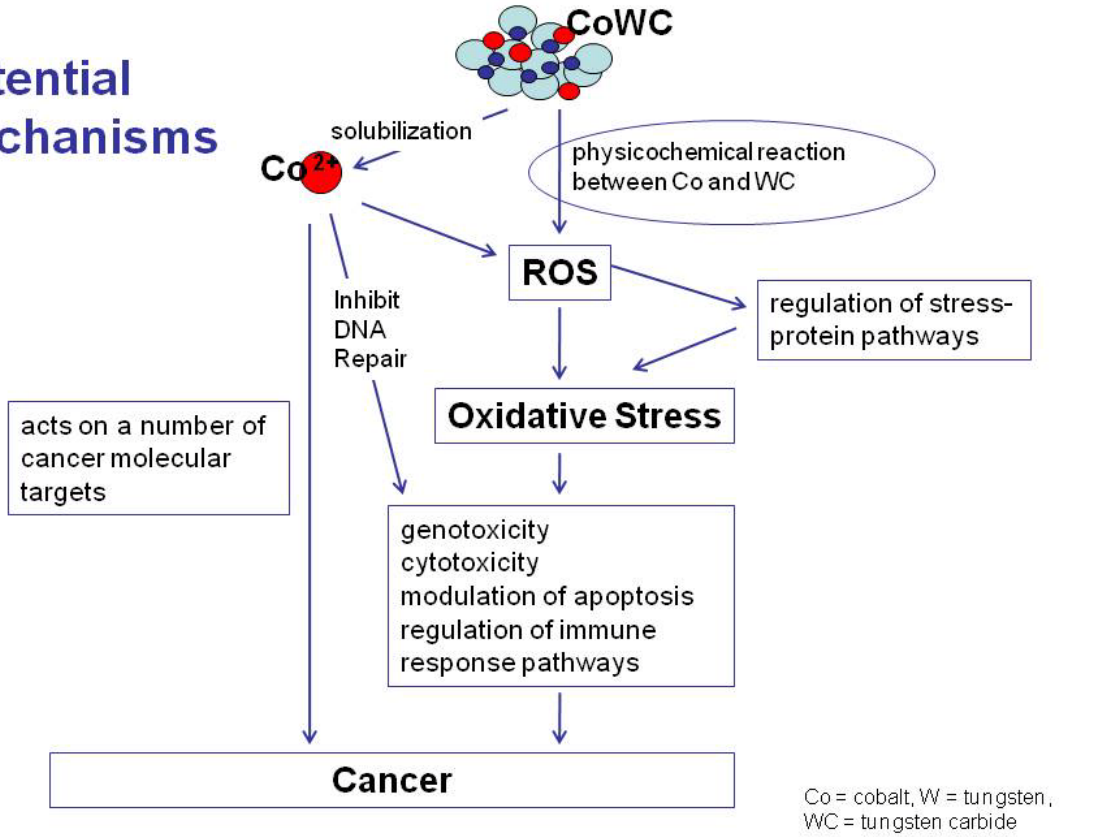
Solubilization of Co from CoWC

- Solubilization of Co and WC from CoWC in cell-free medium
  - After 15 minutes: Co = 77.5 % and WC < 2%
- Co dissolution in different biological fluids (artificial) was similar for pre-sintered and sintered CoWC
  - e.g., solubilities in lysosome:
    pre-sintered = 25.6, post-sintered = 26.7
- WC increases the bioavailability of Co *in vivo* and *in vitro*
  - Rats exposed to CoWC excreted more Co in the urine than rats exposed only to Co
  - In cell free media, the amount of solubilized Co was 4-fold higher from CoWC than pure cobalt
- Co detected in urine, lymph node, lung and other tissues of hard metal workers

Cobalt: Effects

- Inhaled cobalt sulfate causes lung cancer in mice and rats
- Cobalt ions
  - Produce ROS and oxidative damage to DNA
  - Inhibit DNA repair
  - Genotoxic
  - Disrupt cell signaling pathways
  - Regulate genes involved in the response to hypoxia
  - Replace or mimic divalent metal ions altering cellular reactions
  - Modulate apoptosis

Potential Mechanisms



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Cobalt-Tungsten Carbide: Cytotoxicity & Toxicity Studies

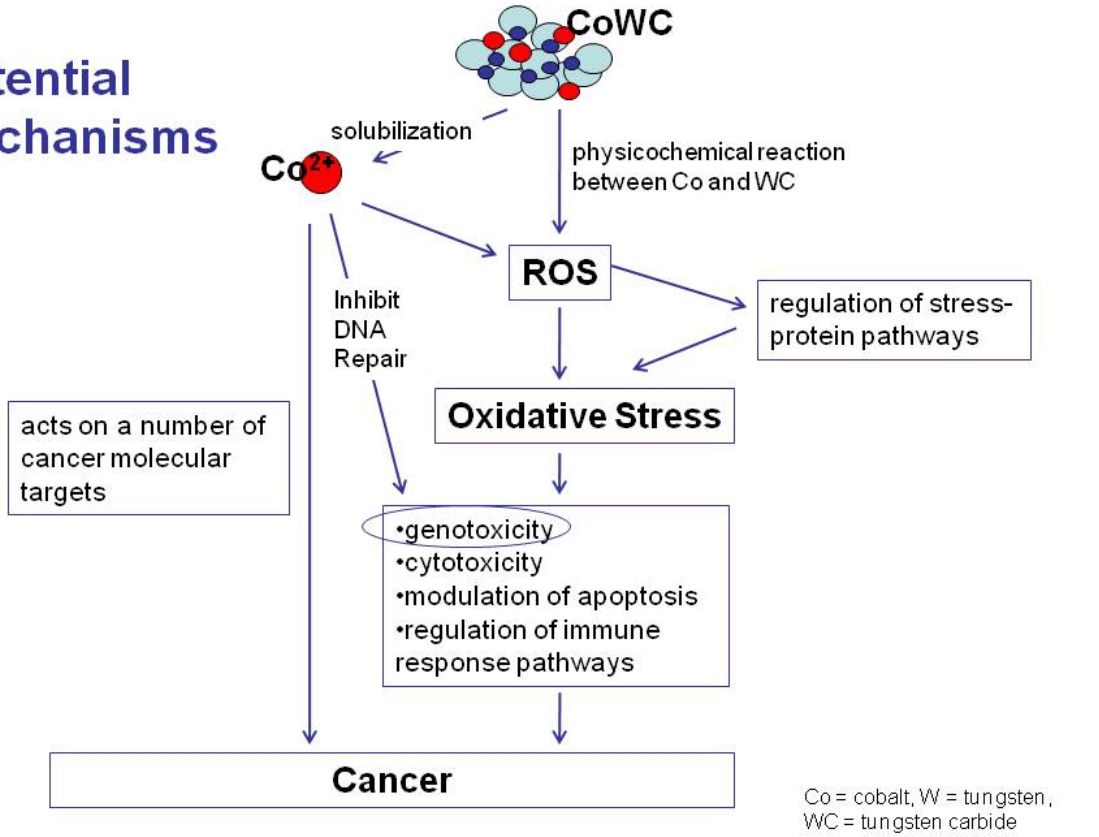
Greater cytotoxic and toxic effects from CoWC than Co or WC alone

- *In vivo* studies in rats after intratracheal administration
  - Two studies reported that CoWC was more cytotoxic (as assessed by LDH, total cells, total protein, & other measures) than Co alone
  - One study reported that both pre-sintered and sintered CoWC caused cytotoxicity in rats
  - Greater toxicity not explained by increased Co bioavailability
- Numerous *in vitro* studies
  - Cytotoxicity usually measured by LDH released
  - Studies in mouse peritoneal macrophages, rat alveolar macrophages and rat type II pneumocytes
  - Cytotoxicity: CoWC > Co > WC

Cytotoxicity & Toxicity Studies (Cont'd)

- Hard metal disease
  - Giant cell interstitial pneumonia leading to fibrosis that occurs in CoWC hard metal workers
  - Both pre-sintered and sintered CoWC can cause fibrosing alveolitis in rats
- Biochemical studies demonstrate greater production of ROS from CoWC compared to Co alone
- Greater toxicity may be result of physicochemical reaction that takes place at the interface between WC and Co
  - Transfer of cobalt electrons to tungsten carbide caused increased oxygen reduction resulting in increased production of ROS

Potential Mechanisms



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Genotoxicity: Clastogenic Effects

- Cobalt-tungsten carbide causes genetic damage in the rat lung (type II pneumocytes)
  - DNA strand breaks and increased micronuclei frequency
- Also causes genotoxicity in cultured cells
  - DNA strand breaks in mouse 3T3 cells and human peripheral blood lymphocytes
  - Increased micronuclei in human peripheral blood lymphocytes
  - CoWC (at cobalt-equivalent concentrations) caused three times as many DNA breaks as cobalt in human peripheral blood lymphocytes
- Cobalt-tungsten carbide workers (small study)
  - Micronuclei formation was associated with working in a CoWC plant, smoking, and DNA repair genotypes; no independent effects

Preliminary Listing Recommendation for the 12th RoC

List cobalt-tungsten carbide: hard metals and powders as *reasonably anticipated to be human carcinogens*

- Limited evidence from studies in humans
  - Demonstrate an association with lung cancer and exposure to cobalt-tungsten carbide
- Mechanistic data demonstrate plausibility and support the findings in humans
  - Cobalt is released from CoWC; inhaled cobalt (soluble) causes lung cancer in experimental animals
  - CoWC and soluble cobalt cause oxidative stress, genotoxicity and act on molecular targets related to carcinogenicity